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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEE, BETTY L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,164	LOOMIS ET AL.	
	Examiner	Art Unit	
	Betty Lee, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-108* is/are pending in the application.

4a) Of the above claim(s) *15,34,42,69,88 and 96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 16-33, 35-41, 43-68, 70-87, 89-95 and 97-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner and Art Unit of application serial number 10693164 has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Betty Lee, Art Unit 1647.

Applicant's election of Group I, claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95 and 97-108, without traverse filed October 28, 2005 is acknowledged. Applicant's election of the species of human angiotensin receptor 2 as the transmembrane receptor, Green Fluorescent Protein (GFP) as the detectable molecule and a U20S cell as the cell species, is also acknowledged; however upon further consideration the requirement for election of species is withdrawn. Claims 15, 34, 42, 69, 88 and 96 are withdrawn from consideration. Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95 and 97-108 are under examination.

Claim Objections

1. Claims 4, 31, 58 and 85 are objected to for a capital letter in "Calcium".

Claims 11, 38, 65 and 92 are objected to for having typographical errors in the words "R_1AR, ~3_2AR, R1AR, f32AR, ~3_1AR, ~3_2AR, ~31AR". There are numerous inconsistencies.

Claim 19 is objected to as having a missing claim number.

Claim 27 is objected to as having a typographical error in the phrase 'dose response curse'.

Claim 73 is objected to as having a typographical error in the phrase 'the est compound'.

Claim 86 is objected to as having a typographical error in the phrase 'natura ligand'. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, 97-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a transmembrane receptor (TMR) agonist wherein the cell such as U2OS cell line expresses an arrestin-GFP conjugate, does not reasonably provide enablement for a method of identifying a transmembrane receptor (TMR) agonist wherein the cell has biologically active fragment of a TMR or where the cell further comprises biologically active fragments of arrestin. Neither is the Applicant enabled for "modifying" the agonist or ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable

one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method of identifying a transmembrane receptor (TMR) agonist, wherein the TMR agonist is capable of activating TMR signaling while exhibiting reduced TMR internalization over a control compound, comprising the steps of providing a cell with at least one TMR or a biologically active fragment thereof, wherein the cell contains arrestin or a biologically active fragment thereof, exposing the cell to at least one test compound, measuring the signaling and the translocation of the TMR at two or more time points and quantitatively determining if the internalization is reduced by comparing the TMR internalization in the presence of a control compound. The invention is further drawn to measurement of the translocation of TMRs (from rat, human, mouse, pig or primate species), specifically, G-protein coupled receptors (GPCR) wherein the GPCR is a class A or class B receptor and the translocation of the TMR is measured by visualization of a radioisotope, an epitope tag, an affinity label, an enzyme, a fluorescent group, or a chemiluminescent group attached to the arrestin or the TMR.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the number of GPCRs within the human genome is estimated to be as great as 1000, and out of 650 identified GPCR genes, only about 190 have been characterized as 'known' GPCRs, which are activated by some 70 identified ligands (Ghosh, *et al.* J. Biomol. Screening 10(5): 476-484, 2005). Orphan GPCRs have unknown or undiscovered ligands. Ligand binding to GPCRs results not only in the activation of G-protein-dependent signaling pathways but also in the induction of pathways that modulate the magnitude and duration of the receptor response.

Cytoplasmic proteins, called arrestins, translocate to and bind the activated receptor at the plasma membrane, thereby attenuating the signaling event. This process is known as desensitization (pg 477, col 1, 1st pgrh). Given that there are thousands of GPCRs in one mammalian species alone, there is a wide variability in structure and function among the classes of GPCRs within the same human species. In addition, Vassilatis, *et al.* (PNAS 100 (8): 4903-4908, 2003) teach that there are 367 human GPCRs for endogenous ligands and 398 mouse GPCRs (pg 4903, Abstract). Therefore, the variability in structure, characteristics and functions of the superfamily of GPCRs between different species such as mouse, rat, pig, primate and human would be even greater.

The amount of direction or guidance present and the presence or absence of working examples: Given the general teachings in the art of that there are hundreds of GPCRs within the human and mouse species, there is insufficient guidance or working examples for the broad claim of identifying ANY TMR agonists from the human, mouse, pig and primate species. The specification does not describe any pig, mouse or primate GPCRs, however, the art teaches that there are hundreds of GPCRs for human and mouse. The specification discloses experiments with rat and human GPCR (Ex. 1) and identifying morphine as μ-opiod agonist (Ex 2) and therefore, the working examples are limited in scope in comparison to the wide range and variety of GPCRs.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability which are found in the art in that there are hundreds of known GPCRs in human and mouse species and orphan GPCRs and the fact that the

specification fails to provide sufficient guidance to overcome the teachings of unpredictability which are found in the art, it would require undue experimentation on the part of one skilled in the art to practice the invention as claimed.

3. Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, 97-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to five genera, i.e.1) the genus of transmembrane receptors (TMR) from rat, human, mouse, pig and primate, (TMR) and biologically active fragments thereof 2) the genus of full-length arrestin and biologically active fragments 3) the genus of control compounds comprising natural

ligands and agonists 4) the genus of test compounds encompassing modified natural ligands and modified agonists and 5) the genus of pharmaceutically relevant compounds.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

There are two species of the claimed genera disclosed that is within the scope of the claimed genera, *i.e. a μ opioid receptor representing the genus of TMR and arrestin-GFP representing arrestin genus.* There are no species disclosed for the genus of control compounds, the genus of test compounds or the genus of pharmaceutically relevant compounds are not disclosed in the specification. The disclosure of a single species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompasses numerous species that are not further described. There is substantial variability among the species. One disclosed species of a μ opioid receptor does not put one in possession of the genus of TMRs rat, human, mouse, pig and primate. One representative opoid receptor has a structure and function that is completely different from another receptor like an adrenergic receptor. The opioid receptor is only one example of a myriad of TMRs that are diverse in structure and function. Their natural ligands do not share a common structure. The specification does not disclose ANY TMRs other than an μ opioid receptor, which is not sufficientlyrepresentative of the broad genus of TMRs from rat, mouse, pig, primate or human TMRs. The TMR superfamily, or more specifically the GPCR superfamily, encompasses thousands of receptors which are different and varied within each species. They run the gamut of neurotransmitter receptors, light receptors, adrenergic receptors, cardiac receptors andhormone receptors. There is considerable variation among the species. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the myriad of GPCRs in the claimed invention. Neither does the description of

arrestin-GFP in the specification shows that the Applicant is in possession of the genus of biologically active fragments of arrestin. There is no description of what constitutes a biologically active fragment e.g. size, number of amino acids, determination of biological activity. There is no disclosure of control compounds or test compounds in the specification. The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 16-33, 35-41, 43-68, 70-87, 89-95, 97-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 28, 55 and 82 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. The instant

claims are incomplete for missing a correlation step. The identification of the agonist is not correlated to the measurement of the translocation of the TMR.

Claims 1, 28, 55 and 82 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase " biologically active" is indefinite because the specification does not define the biological activity of the fragments. Therefore, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 6, 28, 60 and 82 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims cite the word "modified". The metes and bounds of the modifications encompassed within "modified ligands and agonists" are not set forth, so these claims are indefinite.

Claims 7, 33, 61, 87 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "pharmaceutically relevant compounds" is indefinite. The specification fails to set forth how pharmaceutical relevance is determined so as to categorize a compound as pharmaceutically relevant or not.

Claim 4 is indefinite forthe phrase "may be". The phase indicates that the group is not necessarily limited to those which are recited in the Markush group but may encompass other unidentified effectors. Therefore, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claim 20 is indefinite for the phrase "approximately equal". The phrase connotes that the values may differ from each other by some degree; however, the amount or

degree of difference is not set forth. Therefore, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 16, 43, 70 and 97 are indefinite for recitation of a broad limitation in the same claim as a narrow limitation.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 16, 43, 70 and 97 recite the broad recitation “primate TMR”, and the claim also recites “human TMR” which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5,9, 11-13, 16, 20, 55-59, 63-67, 70, 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Barak, *et al.* (US Patent 6110693).

The claimed invention is drawn to a method of identifying a transmembrane receptor (TMR) agonist, wherein the TMR agonist is capable of activating TMR signaling while exhibiting reduced TMR internalization over a control compound, comprising the steps of providing a cell with at least one TMR or a biologically active fragment thereof, wherein the cell contains arrestin or a biologically active fragment thereof, exposing the cell to at least one test compound, measuring the signaling and the translocation of the TMR at two or more time points, or at one or more concentrations of the test compound and quantitatively determining if the internalization is reduced by comparing the TMR internalization in the presence of a control compound. The invention is further drawn to measurement of translocation of TMR (from rat, human, mouse, pig or primate species), specifically, G-protein coupled receptors (GPCR) wherein the GPCR is a Class A or B receptor and the translocation of the TMR is measured by visualization of a radioisotope, an epitope tag, an affinity label, an enzyme, a fluorescent group, or a chemiluminescent group attached to the arrestin or the TMR. The invention is also drawn to the method wherein the control compound is a natural ligand or agonist; wherein the GPCR is opioid, R1AR, ~32AR or dopamine receptor. The invention is also drawn to the method wherein the translocation of the TMR is measured by determining the localization in the plasma membrane, pits,

endosomes, endocytic vesicles or cytosol. The invention is further drawn to the method wherein the signaling is measured at the same time as the translocation is measured; wherein the signaling is approximately equal to or greater than the signaling in the presence of the control compound.

Barak, *et al* teach the method of screening a test compound for GPCR agonist activity wherein a test cell expressing GPCR contains a conjugate of a β-arrestin and a detectable molecule (col 2, lines 58-67). Barak, *et al* teach that due to the therapeutic importance of GPCRs, methods for the rapid screening of compounds for GPCR ligand activity are desirable. Furthermore, Barak, *et al* teach that radiolabeling and fluorescent labeling of test ligands has been utilized in screening for GPCR ligands (col 6, lines 5-17). Barak, *et al* teach a conjugate of a β-arrestin protein and a detectable molecule such as Green Fluorescent Protein (col 2, lines 13-16). Barak, *et al* teach that translocation may be detected by comparing changes in the detectable signal in the same cell over time (i.e. pre and post test compound exposure) or a test cell may be compared to a control cell (no exposure to test compound) or a test cell may be compared to a pre-established method (col 10, lines 18-37). Figs. 6B and 6D shows the agonist-induced time dependent translocation and the dose response curve for the agonist-induced translocation of βarrestin2-GFP to beta2 adrenergic receptors. Fig 6B discloses the measurement of translocation over time and Fig 6D discloses the measurement of signal over different concentrations of the natural agonist, isoproterenol. Barak, *et al* teach that the measurement points may be over time, or among test and control cells (col 15, lines 18-19). Barak, *et al* teach that GPCR

activation with a test compound results in a relative enhancement of the detectable signal at the cell membrane and the concomitant decrease in detectable signal from the cell cytosol (col 10, lines 55-58). In addition, Barak, *et al* teach that exposure to the test compound and the known agonist may occur at essentially the same time, or exposure to the agonist may occur subsequent to exposure to the test compound (col 12, lines 37-40). Barak, *et al* teach that GPCRs include dopamine (GPCR, Class A) (col 14, lines 19-27). Barak, *et al* teach that ten minutes after isoproterenol addition (saturating concentrations), enhancement of membrane fluorescence is accompanied by a concomitant loss of cytosolic fluorescence, indicating that the βarr2-GFP distribution is shifted to the membrane, showing that the β2AR is translocated from the cytosol to membrane following the addition of a βAR2 agonist exhibiting reduced TMR internalization (col 19, lines 56-62).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 7,10, 19, 31-33, 37, 46, 58, 64, 73, 82, 85-87 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barak, *et al.* (US Patent 6110693) in view of Knudsen, *et al.* (WO0246763).

The claimed invention is drawn to a method of identifying a transmembrane receptor (TMR) agonist, wherein the TMRA is capable of activating TMR signaling while exhibiting reduced TMR internalization over a control compound comprising the steps of providing a cell comprising at least one TMR, or a biologically active fragment thereof, wherein the the TMR is a GPCR and signaling is quantitated by measuring an intracellular effector, wherein said effector is cAMP, cyclic GMP, calcium, a lipid, phosphatidylinositol, a hydrogen ion, or an ion transport molecule. The invention is also drawn to a method wherein the GPCR is a Class A or Class B receptor and the control compound is a natural ligand or agonist from a known pharmaceutically relevant compound and the test compound is from a combinatorial library.

As set forth *supra*, Barak, *et al* teach a method of assessing GPCR pathway activity under test conditions, by providing a test cell that expresses a GPCR and that contains a conjugate of a β-arrestin protein and a detectable molecule; exposing the test cell to a known GPCR agonist under test conditions; and then detecting translocation of the detectable molecule from the cytosol of the test cell to the membrane edge of the test cell. Barak, *et al* do not teach a method for identifying an agonist from a known pharmaceutically relevant compound and do not teach that the test compound is from a combinatorial library.

Knudsen, *et al.* teach that GPCRs represent a large superfamily of proteins that transduce extracellular signals to the interior of cells, wherein each individual GPCR type activates a particular signal transduction pathway. Knudsen, *et al.* teach that activation of GPCRs may be determined by measuring the level of cAMP, Ca^{2+} or via

the ^{35}S-GTPγS assay (pg 3, lines 32-34). Knudsen, *et al.* teach examples of Class A (β 2-adrenergic receptors, dopamine D1a receptor, opioid receptors and serotonin receptors) and Class B (angiotensin) receptors (pg 5, lines 17-23). Knudsen, *et al.* teach that test compounds are preferably obtained from libraries and may be peptides or other organic molecules and they may be organized according to standard methods into systems or arrays enabling a systematic testing of possible variations of chemical compositions such that several test compounds are contacted with cell membrane preparation in the same vessel. In addition, Knudsen, *et al.* teach that chemical libraries, such as combinatorial chemical libraries, comprise chemical compounds that have been synthesized from a systematic series of reactions (pg 6, lines 1-7). Knudsen, *et al.* teach that a control compound can be any kinase phosphorylating a given GPCR and there are at least six members of the G-protein coupled receptor kinase (GRK) (pg 7, lines 16-26) which are considered natural ligands or agonists.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method as taught by Barak, *et al* to test compounds from combinatorial libraries as taught by Knudsen, *et al.* The person of ordinary skill in the art would have been motivated to modify the methods of Barak to test compounds from combinatorial libraries for potential agonists because the search for new agonists for GPCRs for therapeutic use have been the emphasis for pharmaceutical companies in recent years.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Betty Lee, Ph.D. whose telephone number is (571) 272-8152. The examiner can normally be reached on M-F 9 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BLL

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